REMARKS

Claims 52-53, 55, and 60 are pending.

Claims 1-51, 54, 56-59, and 61 have been cancelled.

Claim 52 have been amended to clarify the invention.

Support for the amendments is found in the claims and specification (*e.g., see* the Examples on pages 12-16) as originally filed. No new matter is believed to have been added.

Claims 52-53, 55, and 60-61 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The rejection focuses on two main points (A) delivering therapeutic level of antibodies and (B) gene therapy is unpredictable.

Applicants need not directly address these points as they are largely misplaced to what is claimed.

The claimed method is not a method of treating disease X or providing therapeutic levels of antibodies in a mammal. The claimed method is simply to delivering an antibody. There cannot be any dispute that the application as originally filed enables delivering an antibody following the method steps defined in the claims.

More specifically, the claimed method is directed to a novel generic mode for administration of monoclonal antibodies (mAbs), which is independent of the nature of the administered antibody. Similarly, the development of a new syringe would be independent of the molecules that it would contain when used to treat patients. The main point of the invention is to demonstrate that a monoclonal antibody can be produced by genetically-modified non-B cells in a living mammal and that this mAb can be distributed systemically, as shown by its presence in the blood circulation, without inducing significant adverse against the mAb, *i.e.*, inducing an anti-idiotypic response capable of neutralizing it (*see* the Examples).

The Examiner's reliance in the rejection of producing a "therapeutic" level of an antibody is misplaced because the claimed method is directed to a method of **delivering** an antibody into a subject and if it is done the way it is claimed, one will produce an antibody via transplantation of non-B cells producing the antibody and no anti-idiotypic response will be triggered. The method does not require treating a disease with this antibody similar to a new syringe that delivers a substance into a subject without a requirement to treat a disease, if any, in the subject with this substance.

To answer the Examiner's assertion regarding unpredictability, in the description of the invention, the inventors resorted to (i) a model antibody (Tg10) presenting a number of advantages (*e.g.*, mouse origin, cloned and characterized in the laboratory, availability of a very sensitive ELISA, availability of methods to study a possible anti-idiotypic response against it, which is extremely rare, availability of reliable methods to assess its thermodynamic and kinetic properties in complex biological fluids such as serum) to prove the concept and (ii) vectors, expression cassettes and grafting procedures.

Concerning the latter point, vectors, expression cassettes and grafting procedures used by the inventors were known and amongst the most efficient and widely used ones at that time. Also, Noel et. al. (Human Gene Therapy 8: 1219-1229, 1997; last line of page 1227 and most of page 1228) cited previously, extensively discuss possible lines of improvements for both the vectors and the expression cassettes with suggestions for future improvements.

Further, obtaining a nucleotide sequence encoding an antibody, cloning the sequence into an expression vector using a known promoter and elements providing secretion of the antibody, and transplantation techniques are well known in the art (*see* the specification, pages 1-10). Using these tools, the inventors have demonstrated the feasibility of the systemic delivery of mAbs keeping their functional properties in a living mammal through

genetic *ex vivo* modifications of non-B cells (*i.e.*, cells not naturally producing antibodies) that could be used in gene/cell therapy protocols.

Initially Applicants wanted to find out whether various cell types that do not specialize in antibody production and can be grafted (*e.g.*, hepatocytes, skin cells, fibroblasts, muscle cells, etc.) and used in gene- or cell-therapy procedures, might produce a recombinant monoclonal antibody. The cultured lines, *i.e.*, NIH 3T3 in mice in the case of fibroblasts, human A431 in the case of keratinocytes, human HepG2 in the case of hepatocytes and C2C12 cells in mice in the case of muscle cells, were used. These findings were reported in the present specification as well as in the paper by Noël et al. (HTG, 1997). In this paper, it was also shown that antibodies could be produced *ex-vivo* by primary cells (human hepatocytes, mice fibroblasts and muscle cells in mice) following genetic modification. Subsequently, it was also reported that primary human keratinocytes could also produce correct antibodies *ex-vivo* (Noël et al., JID 2002).

Applicants then turned to the mouse since this is the most congenial animal for laboratory experimentation; it is used extensively as the pre-clinical model with a view to developing treatments for humans. Applicants have initially used the "myoblast graft" model using the C2C12 line, and conducted experiments on histo-compatible syngeneic mice in order to prevent rejection. It was known that this line was tumorigenic and hence prone to produce tumors. This was not a problem at the concept-testing phase and did not cast doubt on the main objective of the research. It was shown that genetically-modified C2C12 cells were capable of producing antibodies systemically before the onset of tumors, which appeared only some months after the graft (and not always then). This work is described in the specification as well as the paper by Noël et al. (HGT, 1997). The research was first supplemented by non-tumorigenic primary myoblasts (Noël et al., HGT, 1997). Similar grafting experiments with genetically-modified cells were then successfully conducted with

skin fibroblasts (Noël et al., JID, 2000) and with keratinocytes (Noël et al., JID, 2002). For hepatocytes, gene-transfer experiments through a direct injection of recombinant adenoviruses in mice were conducted (Noël et al., HGT, 2002). Thus, Applicants provide sufficient experimental data to enable the claims with respect to several different cell types (*see* claim 53).

The Examiner also believes that Qu et al., Hortland et al., and Bendandi et al. support her assertion that production of a foreign antibody in a subject without triggering an anti-idiotypic response is unpredictable.

In response, Applicants point out that in no way do Qu et al. assert that it is impossible to successfully graft myoblasts. Essentially, Qu et al. show that populations of primary myoblasts are heterogenous, and the likelihood that some, but not all, sub-populations will survive is low. Thus, Qu et al. support the Applicants' view that it is possible to graft myoblasts. Indirectly, Qu et al.'s work also suggests that there is significant room for further improvement to myogenic cell-grafting procedures. In this respect, Qu's et al. position is not different from that of most biotherapies. Also, in this application, it is essential to remember that the claims do not go beyond grafting cells that are compatible with the recipient (*see* claim 52).

Concerning eliciting an anti-idiotypic response, it demands specific conditions (most likely inflammatory). On page 3 line 2 of the Official Action, the Examiner uses the word "avoided" to imply that Applicants ought to be suggesting something specific to prevent an anti-idiotypic response from being elicited against ectopic mAb, sufficient to neutralize the latter. The facts of the case are quite otherwise. At the time Applicants began their experiments, it was legitimate to be concerned about this possibility. Before resorting to complicated protocols/procedures, Applicants used the most direct gene-transfer and cell-grafting methods possible. It was a pleasant surprise to find there was no need to do anything

special to prevent the onset of an anti-idiotypic response against the ectopic antibody. In other words, the therapy-administration conditions are not sufficiently immunogenic to elicit an anti-idiotypic response.

In a paper by Pelegrin et al. cited previously (Gene Therapy, 1998), 13 mice were immunized with the Tg10 model mAb described in the invention, together with Freund's adjuvant (a strong inflammatory adjuvant). Even under this particularly favorable condition with respect to anti-idiotypic response induction, only 6 mice developed any detectable anti-idiotypic response. The Bendandi et al. review also discusses repeatedly the necessity of an adjuvant in order to elicit an anti-idiotypic response (*see*, the chapters "Current strategies for the production of an anti-Id vaccine" (p1334), "Soluble protein Id vaccine in clinical trials" (pl335), and "DNA vaccine trials" (p1336) and yet again in the concluding paragraph, in which the authors emphasize that a wide-ranging enquiry into the elicitation of the anti-idiotypic response is the best "vaccine formulation"). Thus, Pelegrin et al. and Bendandi et al. back up the Applicant's argument that it is extremely difficult to elicit an anti-idiotypic response. Specifically, an anti-idiotypic vaccine needs to be made far more immunogenic than it is in its free form (Bendandi et al., page 1334, right col., first and second full paragraphs). For this purpose, the vaccine may be conjugated with a highly immunogenic carrier. *Id.* Also, the association of a soluble protein Id vaccine with immunogenic adjuvants is extremely important. *Id.*

Applicants conducted experiments on gene antibody transfers *in-vivo*, using various doses of recombinant adenoviruses (*see* the Examples). They did not observe any anti-idiotypic response, except in two mice injected with very high doses of adenovirus equivalent to inflammatory (and hence immunogenic) situations, up to the limit the animal was able to tolerate. However, these responses were at least a thousand times lower than the ectopic mAb level, *i.e.*, was insufficient to neutralize the latter mAB *(see* the Examples).

Concerning Hortelano et al., the authors implanted C2C12 cells producing factor IX into mice with the aid of micro-capsules. They then found that tumors had appeared after 6 weeks. Thus, the question is one of finding out whether, in the present application, the antibody is produced by non-tumorous cells after two months and not by tumorous cells.

In order to encapsulate the C2C12 myoblastic cells secreting factor IX, Hortelano et al. used alginate capsules. This involves tiny spheres made from a substance extracted from alga. The cells are trapped within. However, this substance is not very solid and disintegrates quite rapidly. This explains why C2C12 cells escaped and were able to produce tumors in some animals.

Hortelano et al. conducted experiments on nude immuno-deficient mice, whereas Applicants' experiments were conducted on non-immuno-compromised mice. These were syngeneic in order to prevent any rejections of grafted cells. Nude mice are among the most sensitive *in- vivo* methods used to test the tumorigenicity of tumorous cells (and indeed to preserve tumors that prove impossible to replicate under usual cell-culture conditions). Thus, it is entirely logical that tumors appeared rapidly in these animals. By contrast, the C3H mice of the present applications do not all develop tumors when grafted with C2C12 cells, and when tumors do occur, they cannot be detected before 3-4 months under the experimental conditions Applicants used. This gives an ample time to assess whether the gene or cell therapy works. Moreover, if antibody production were associated with proliferating tumorous cells (and not the muscle, which fails to proliferate following fusion of myoblasts with resident muscle fibers), it is likely that Applicants would have seen an increase in the concentration of the Tg10 mAB (linked to the increase in the number of productive cells) in their animals, as a function of time. This was not the case.

As stressed by Hortelano et al., C2Cl2s cells are known to be tumorigenic. However, this did not preclude C2C12s from being among the best cell systems at the time of the

invention to facilitate muscle formation after grafting to histo-compatible mice (grafted myoblasts fuse rapidly with resident muscle fibers to create muscle).

It is essential here to stress certain points. Firstly, the results presented in the specification and in the paper by Noël et al. (HGT, 1997) refer to animals that had not yet developed any tumors. Secondly, C2C12s show some characteristics that vary noticeably from one laboratory to another, especially with regard to tumorigenicity. This might explain, at least in part, why Applicants got no tumors at 6 weeks. Thirdly, procedures for the administration of genetically-modified cells differed between the two laboratories. In the case of Hortelano et al., the cells were implanted into a substance (capsules) that isolated them from the animal. Also, the implantation of the capsules were performed at the location which is not muscle, which may have favored tumor development. In this application, the modified cells were grafted into the treated animals so as to stimulate regeneration of muscle fibers at the very locus of the C2C12 myoblast graft. This promotes fusion with resident muscle fibers and delays - or possibly prevents - onset of tumors. Moreover, the Applicants' initial experiments with the C2C12 cells were quickly corroborated by experiments with primary myoblasts (Noël et al., HGT 1997), which develop tumors only rarely (except when they are brought about disproportionately by being cultured *ex vivo* for long period of time). In conclusion, there are no grounds for believing that the Tg10 mAb could have been produced by a tumor rather than by a muscle fiber with which genetically-modified cells would have fused.

Applicants request that the enablement rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

M. Miller

Marina I. Miller, Ph.D.
Attorney of Record
Registration No. 59,091

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/07)